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Albert Einstein Centre
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Nottingham, NG7 2TN
United Kingdom

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom 6946729001

4. Title of the invention

COLONIC DELIVERY OF WEAK ACID DRUGS

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

ERIC POTTER CLARKSON
ST MARY'S COURT
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NG1 1LE

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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11. I/We request the grant of a patent on the basis of this application.

Signature Eric Potter Clarkson Date

ERIC POTTER CLARKSON 3 October 1996

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COLONIC DELIVERY OF WEAK ACID DRUGS

Drugs that have weak basic functions and/or weak acid functions with pKa values of 3.0 - 9.0 often have a low and variable solubility at the colonic pH range of 5-8. Consequently, if the drug is delivered to the colon for, for example, local action, the dissolution of the drug from the tablet, pellet or capsule formulation can be extremely variable and satisfactory controlled release profiles are not obtained. Ridogrel, Janssen Pharmaceutica, Belgium ((E)-5-[[[3-pyridinyl[3-(trifluoromethyl)phenyl]methylene] amino]oxy]pentanoic acid) is an example of such a drug.

Ridogrel is a new compound that could have benefit in the treatment of inflammatory bowel disease to include Crohn's disease and ulcerative colitis. The drug can be administered orally in simple pharmaceutical formulations. However, advantage would be gained if the drug could be delivered to the colonic environment in a slow release fashion. Delivery to the colon will concentrate the drug at the required site of action and therefore prevent unwanted absorption of the drug into the systemic circulation from the small intestine. The controlled release nature of the formulation will provide good access of the drug to the various regions of the large intestine.

Methods for the site specific delivery of drugs to the large bowel have been described in the prior art, to include our pending patent (PCT/GB95/01458) on the coating of starch capsules with polymers that degrade or dissolve under the conditions found within the different regions of the gastrointestinal tract. A preferred system was a starch capsule coated with a mixture of methacrylate polymers. These polymers start to dissolve once the pH is above 5, thereby allowing a formulation to remain intact in the stomach but upon entry into the small intestine, the coating on the capsule begins to dissolve. By adjustment of the thickness of the coating, it is possible for the capsule to reach the terminal ileum or ascending colon before releasing its contents. Another granted patent describes how a similar effect can be achieved using polymers that are degraded specifically in the colonic environment due to the unique reducing conditions therein. Polymers based upon disulphide bonds have been shown to be effective both *in vitro* and *in vivo* (PCT/BE91/00006).

Alternatively, the composition can be delivered to the colon using other known colon targeting systems. Some examples, which are not exhaustive are as follows.

The Time Clock Release System™ (Pozzi et al. APV Course on Pulsatile Drug Delivery, Konigswinter, 20 May 1992) is a tablet system where a tablet core containing the active drug is coated with a layer of pharmaceutical excipients. The excipients hydrate causing the surface

layer to burst at a set time. The Pulsincap™ system is an oral pulsatile delivery system which may be configured to release its drug content at a predetermined time or place within the gastrointestinal tract. The device essentially consists of an impermeable capsule body which contains the drug, sealed at the neck orifice with a hydrogel plug. A normal gelatin cap is then placed on to the body of the device. After ingestion the gelatin cap dissolves allowing the plug to hydrate. At a predetermined and controlled time the swollen plug is ejected from the body of the device, thereby releasing the capsule contents and enabling the drug to be released. (Wilding et al., Pharm. Res. 9, 654, 1992 and Binns et al., 3rd Eur. Symp. Control. Drug Del., Abstract Book, 1994, p124).

Another system which may be used is the time controlled explosion system as in US 4871549 (incorporated herein by reference).

The problem with the drug Ridogrel and similar molecules is one of achieving a controlled release formulation that will spread in the colon to give maximum treatment of affected sites and for such release to be constant and predictable over an extended period of time.

Controlled release formulations of drugs in the colon can also be useful for the systemic delivery of therapeutic agents as once daily products.

The controlled release of drugs that are weak acids or weak bases can be achieved using a variety of mechanisms. However, in order to have a formulation that spreads well at the target site, a multiparticulate pellet formulation is to be preferred. Pellets can be formed by a number of different processes, to include extrusion and spheronisation as well as the coating of the drug material onto preformed sugar spheres (also known as non-pariels). The drug can be coated onto the beads using techniques familiar to those skilled in the art. A controlled release layer can then be coated on top of the drug layer so as to provide a diffusional barrier. Unfortunately, with drugs such as Ridogrel, a simple diffusional barrier does not provide a satisfactory product. Ridogrel has weakly basic functions and a carboxylic acid function and the solubility of the drug in the colonic pH range (5-7) is low. As a consequence, the solubility of the drug at such a pH and the consequent dissolution of the drug can be extremely variable. Thus a simple formulation, wherein Ridogrel is coated onto non-pariel beads and then overcoated with a rate-controlling membrane, does not result in a satisfactory release profile.

We have found surprisingly, that it is possible to achieve a satisfactory coated pellet formulation for Ridogrel by choosing instead of the drug itself, an appropriate alkali metal salt form that has pH independent solubility characteristics. The salt of the drug should be at least 10 x more soluble than the free acid form of the drug and more preferably more than 100 X as soluble. It

is then found surprisingly that the coated pellet system gives an almost pH independent release profile under *in vitro* conditions as tested in the USP type 2 dissolution apparatus (The United States Pharmacopoeia, USP23, 1994, page 1791-1793). Thereafter, the adjustment of the nature of the coating material and the thickness of such a coating material can be altered to provide a controlled release formulation that for example, will release the drug over a period of up to 5 hours or over a longer period of up to 12 hours.

Suitable salts of the weak acid drugs are alkali metal salts such as but not limited to sodium and potassium salts. The salts can typically be prepared by dissolving the drug in a solution of the hydroxide of the alkali metal. An excess of drug is suspended in the hydroxide solution and stirred for 24 hours. The suspended material is removed by filtration and centrifugation and the salt recovered from the filtrate by removal of the water eg. using a vacuum oven or by lyophilisation. The salts can also be prepared as part of the preparation process for the coating of the pellets. In this case the drug is dissolved in for example sodium hydroxide solution (1M) and the pH is adjusted to 8 by adding 0.1M HCl. The salt solution is added to a solution of povidone (binder) and the pH again adjusted to 8. This mixture is then coated onto the sugar spheres using for example a spray coating equipment. The pellets can if necessary be overcoated with a thin layer of plasticised HPMC. These pellets are then overcoated with the controlled release coating layer for example consisting of Eudragit RS30D, triethyl citrate and talc and dried. The pellets can then be filled into capsules to be coated for delivery to the colon or compressed into tablets which are then coated.

The preferred controlled release coating material is one which forms a water-insoluble but water-permeable layer and from which release of drug is by diffusion through the layer. The coating polymer may be inherently water-permeable or become water-permeable through the incorporation of other additives such as plasticisers or pore forming agents. Such polymers include methacrylate copolymers, ethylcellulose, etc. Preferred coating materials are the permeable, water insoluble grades of pharmaceutical polymethacrylates (Eudragit® RL100, Eudragit® RS100, Eudragit® NE30D, Röhm Pharma, Darmstadt, Germany) and ethylcellulose. Eudragit RL100 and RS100 contain quaternary ammonium groups which may interact with ionised weakly acidic drugs and hence the most preferred coating materials are ethylcellulose and Eudragit NE30D. Ethylcellulose may be applied as a solution in organic solution or as a proprietary water-based latex preparation (eg. Aquacoat®, FMC, Philadelphia, USA or Surelease®, Colorcon, West Point, USA). The thickness of coating needed will depend on the permeability of the polymer to the drug in question and the duration of release required from the coated formulation but will typically be in the range 2% w/w to 25% w/w of formulation or in the range 80μm to 300 μm. The thickness of the particular coating used will be chosen according to the mechanism by which the coating is dissolved.

The coated pellets so described in this invention, can be filled into the various known delivery systems intended for colonic targeting described above, to include the coated capsules described above. Alternatively, the pellets can be further coated with an enteric layer that slowly dissolves within the small intestine to allow exposure of the rate limiting membrane to the liquid in the terminal ileum or the colon for subsequent release. In similar fashion to the coated starch capsules, the coating may be an enteric polymer that dissolves in the small intestine or a polymeric or polysaccharide material that is not degraded until it meets the specific conditions found in the colon. Such degradation may be through direct chemical effect, eg the degradation of disulphide bonds under reducing conditions, or the degradation of polysaccharide materials under the effects of the microflora found within the colon.

Preferred coating materials for the capsules, tablets or the pellets for targeting to the colon are those which dissolve at pH of 5 or above. The coatings therefore only begin to dissolve when they have left the stomach and entered the small intestine. A thick layer of coating is provided which will dissolve in about 3-4 hours thereby allowing the capsule underneath to breakup only when it has reached the terminal ileum or the colon. Such a coating can be made from a variety of polymers such as cellulose acetate trimellitate (CAT), hydroxypropylmethyl cellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP) and shellac as described by Healy in his article "Enteric Coatings and Delayed Release" Chapter 7 in Drug Delivery to the Gastrointestinal Tract, editors Hardy *et al.* Ellis Horwood, Chichester, 1989. For coatings of cellulose esters, a thickness of 200-250μm would be suitable.

Especially preferred materials are methylmethacrylates or copolymers of methacrylic acid and methylmethacrylate. Such materials are available as Eudragit® enteric polymers (Rohm Pharma, Darmstadt, Germany). These are copolymers of methacrylic acid and methylmethacrylate. Preferred compositions are based on Eudragit L100 and Eudragit S100. Eudragit L100 dissolves at pH 6 and upwards and comprises 48.3% methacrylic acid units per g dry substance; Eudragit S100 dissolves at pH 7 and upwards and comprises 29.2% methacrylic acid units per g dry substance. Preferred coating compositions are based on Eudragit L100 and Eudragit S100 in the range 100 parts L100:0 parts S100 to 20 parts L100:80 parts S100. The most preferable range is 70 parts L100:30 parts S100 to 80 parts L100:20 parts S100. As the pH at which the coating begins to dissolve increases, the thickness necessary to achieve colon specific delivery decreases. For formulations where the ratio of Eudragit L100:S100 is high, a coat thickness of the order 150-200μm is preferable. This is equivalent to 70-110 mg of coating for a size 0 capsule. For coatings where the ratio Eudragit L100:S100 is low, a coat thickness of the order 80-120μm is preferable, equivalent to 30 to 60 mg coating for a size 0 capsule.

The colonic region has a large population of microbial anaerobic organisms providing reducing conditions. Thus the coating may suitably comprise a material which is redox-sensitive. Such coatings may comprise azopolymers which can for example consist of a random copolymer of styrene and hydroxyethyl methacrylate, cross-linked with divinylazobenzene synthesized by free radical polymerization, the azopolymer being broken down enzymatically and specifically in the colon, or disulphide polymers (see PCT/BE91/00006 and Van den Mooter, Int. J. Pharm. 87, 37, 1992).

Other materials providing release in the colon are amylose, for example a coating composition can be prepared by mixing amylose-butan-1-ol complex (glassy amylose) with Ethocel aqueous dispersion (Milojevic *et al.*, J. Control. Rel. 38, 75-84, 1996), or a coating formulation comprising an inner coating of glassy amylose and an outer coating of cellulose or acrylic polymer material (Allwood *et al.*, GB9025373.3), calcium pectinate (Rubenstein *et al.*, Pharm. Res., 10, 258, 1993) pectin, a polysaccharide which is totally degraded by colonic bacterial enzymes (Ashford *et al.*, Br. Pharm. Conference, 1992 Abstract 13), chondroitin sulphate (Rubenstein *et al.*, Pharm. Res. 9, 276, 1992) and resistant starches (Allwood *et al.*, PCT WO89/11269, 1989), dextran hydrogels (Hovgaard and Brøndsted, 3rd Eur. Symp. Control. Drug Del., Abstract Book, 1994, 87) modified guar gum such as borax modified guar gum (Rubenstein and Gliko-Kabir, S.T.P. Pharma Sciences 5, 41-46, 1995), β-cyclodextrin (Sie ke *et al.*, Eu. J. Pharm. Biopharm. 40 (suppl), 335, 1994), saccharide containing polymers, by which we include a polymeric construct comprising a synthetic oligosaccharide-containing biopolymer including methacrylic polymers covalently coupled to oligosaccharides such as cellobiose, lactulose, raffinose, and stachyose, or saccharide-containing natural polymers including modified mucopolysaccharides such as cross-linked chondroitin sulfate and metal pectin salts, for example calcium pectate (Sintov and Rubenstein PCT/US91/03014); methacrylate-galactomannan (Lehmann and Dreher, Proc. Int. Symp. Control. Rel. Bioact. Mater. 18, 331, 1991) and pH-sensitive hydrogels (Kopecek *et al.*, J. Control. Rel. 19, 121, 1992). Resistant starches, e.g. glassy amylose, are starches that are not broken down by the enzymes in the upper gastrointestinal tract but are degraded.

While this invention is mainly directed to the drug Ridogrel, other drugs that are delivered to the colon using a controlled release mechanism are also part of this invention and could be incorporated into the formulation. This is particularly true for those drugs that have a rapidly changing solubility in the pH range 5-7. This is the pH range found in the colon under normal conditions, although it has been reported in acute conditions such as ulcerative colitis, the pH in the proximal colon can be as low as pH 4.5. Drugs that would be suitable for inclusion in the invention are those that have a pKa within the critical region of pH 3.0 - 9.0 and which can be converted into alkali metal salts.

Example 1 (Comparative example)

Preparing ridogrel pellets coated with polymethacrylate (Eudragit RS)

A solution of 20 g of ridogrel (Janssen Pharmaceutica, Belgium) and 2 g of povidone (Kollidon 30) in 250 ml of ethanol was prepared. This solution was spray-coated onto 400 g of sugar spheres (600-710 μm, NP Pharma, France) using an Aeromatic STREA-1 coater. The pellets were assayed for ridogrel content by a spectrophotometric method. To prepare the coating solution of sustained release polymer, 35 g of talc was first dispersed in 250 ml of water and 9 g of triethyl citrate added. 150 ml of Eudragit RS30D (Rohm Pharma) was then added to the talc dispersion. 280 g of the ridogrel-coated pellets were coated with the Eudragit solution in the STREA-1 using an inlet temperature of 50°C. 100 ml of solution was applied to the pellets. The pellets were then dried overnight at 40°C and assayed for ridogrel content using a spectrophotometric method.

The dissolution performance of the pellets was measured using the BP/USP method 2 (USP23, 1994, page 1791-1793) (paddles, 50 rpm) with 900 ml of either pH 6 or pH 7 phosphate buffer as the test medium. In Figure 1 the dissolution performance of the pellets is shown. Compared to the performance of the pellets at pH 7 there was a substantial reduction in the rate of drug release at pH 6. For example, after 4 hours approximately 24% of the ridogrel had been released at pH 6, compared to 74% at pH 7.

Example 2

Solubility of ridogrel and sodium ridogrel

In accordance with the invention, sodium ridogrel was prepared as follows:

i) 0.1 g of sodium hydroxide was dissolved in 20 ml of water.

ii) 1.5 g of ridogrel was added to the sodium hydroxide solution to form a suspension.

iii) The ridogrel suspension was placed into a sonic bath for 10 minutes.

iv) The suspension was passed through a 0.45 μm membrane filter. The filtrate was collected, diluted by adding 20 ml of water and lyophilised overnight.

v) The lyophilised sodium ridogrel was gently milled in a mortar to produce a fine powder.

Into each of three size 2 hard gelatin capsules was weighed 10 mg of ridogrel. Into another three capsules was weighed 10 mg of the sodium ridogrel lyophilisate. The dissolution of ridogrel and sodium ridogrel into 900 ml of phosphate buffer at pH 5, 6 and 7 was tested (USP apparatus 2, 100 rpm). The dissolution rate of ridogrel (as the parent acid) increased as the pH was raised (Figure 2a). In contrast, the rate of dissolution of sodium ridogrel was largely independent of pH (Figure 2b).

Therefore there was a significant reduction in the rate of dissolution of ridogrel as the pH was reduced from 7 to 5, the pH range likely to be encountered in the large intestine. However, in this pH range, the sodium salt of ridogrel had a greatly improved dissolution rate.

Example 3

Preparation of pellets coated with sodium ridogrel and Eudragit

Pellets were prepared containing the sodium salt of ridogrel. 20 g of ridogrel was dissolved in approximately 60 ml of 1M sodium hydroxide solution. The solution of sodium ridogrel was adjusted down to pH 8 by adding 0.1M hydrochloric acid and made up to 100 ml with water. 40 g of povidone (Kollidon 30, BASF) was dissolved in 200 ml of water. The povidone solution was added to the ridogrel solution and a precipitate was formed which was dissolved by adding sodium hydroxide to adjust the solution to pH 8. The povidone/ sodium ridogrel solution was applied to 1 kg of sugar spheres (0.6-0.71 mm) using the Aeromatic STREA-1 coater. After coating, the pellets were relatively tacky which could have been due to the hygroscopic nature of the povidone and/or the sodium ridogrel. To remove this tackiness, the pellets were overcoated with a thin layer of HPMC: The HPMC solution was prepared by dissolving 30 g of Methocel E5 in 600 ml of water and adding 3 g of PEG400 as a plasticiser. The pellets were assayed for ridogrel content.

450 ml of Eudragit coating solution was prepared as follows: 150 ml of Eudragit RS30D, 9 g of triethyl citrate, 35 g of talc, 250 ml of water. The solution was applied to 400 g of sodium ridogrel/povidone/HPMC pellets. The coated pellets were dried overnight at 40°C. The pellets were assayed for ridogrel content.

The dissolution performance of the pellets at pH 5, 6 and 7 is shown in Figure 3. There was a small reduction in the rate of drug release as the pH was decreased. This demonstrated that the rate of release of ridogrel as the sodium salt was largely independent of pH, which was in marked contrast to pellets containing ridogrel as the parent acid (see Figure 1).

Example 4

Preparation of pellets coated with sodium ridogrel and ethylcellulose

Pellets were prepared with an ethylcellulose outer layer. A water-based ethylcellulose preparation, Aquacoat® (FMC, Philadelphia), was used in order to eliminate the use of organic solvents in the coating process. Pellets were prepared as follows:

20 g of ridogrel was weighed into a beaker and dissolved in 56 ml of 1M sodium hydroxide solution. 40 g of povidone (Kollidon K30) was weighed into a large beaker and dissolved in 500 ml of water. The ridogrel solution was added to the povidone solution. The pH change resulted in precipitation of ridogrel. Sodium hydroxide solution was added to dissolve the

ridogrel. The pH of the solution was adjusted down to pH 8 using 0.1M hydrochloric acid and made to 600 ml with water. 1 kg of sugar spheres (1.00-1.18 mm diameter) were coated with the sodium ridogrel/povidone solution using the Aeromatic STREA-1 coater (inlet temperature = 55°C). An overcoat of HPMC was applied to the sodium ridogrel/povidone layer: The HPMC solution was prepared by dispersing 20 g of HPMC (Methocel E5) in 200 ml of hot water. The dispersion was cooled in ice while stirring and 2 g of PEG400 added as a plasticiser. The solution was made up to 400 ml with water. The HPMC solution was applied using the STREA-1 at an inlet temperature of 55°C. The completed pellets were left to dry overnight at room temperature. The Aquacoat mixture was prepared by stirring together 300 ml of Aquacoat and 21.6 g of dibutyl sebacate for 1 hour, followed by the addition of 300 ml of water. 500 g of sodium ridogrel/povidone/HPMC pellets were transferred to the Aeromatic and coated with the Aquacoat mixture (coating temperature = 40°C). Pellet samples (20 g) were collected at intermediate points in the coating run, after the application of approximately 300 ml and 450 ml of the coating solution. After coating, the pellet samples were spread into trays and dried overnight at 60°C.

The dissolution performance of the pellets at pH 7 is shown in Figure 4. The dissolution performance of the pellets containing 14% coating at pH 5, 6 and 7 is shown in Figure 5. Drug release was independent of pH. The release of drug from these samples was complete. This was in contrast to the Eudragit-coated pellets where drug release was incomplete. This was probably due to an interaction between negatively-charged ridogrel ions and positively charged quaternary ammonium groups within Eudragit RS. Hence ethylcellulose is the polymer-of-choice for preparing ridogrel controlled release pellets.

Claims

Claim 1 A controlled release formulation comprising an inner core containing or coated with a drug and subsequently coated with a rate-controlling membrane that determines drug release, of a drug that contains a weak acid function with a pKa in the range 3-9 that can be converted into an alkali metal salt wherein the drug is present as a salt that displays higher solubility at pH 5.0 - 7.0 than the corresponding compound containing a free acid.

Claim 2 A composition as described in Claim 1 where the drug is Ridogrel.

Claim 3 Composition as described in Claim 1 where the drug is used for the treatment of ulcerative colitis, Crohn's disease, irritable bowel syndrome, inflammatory bowel disease.

Claim 4 A composition as described in Claim 1 where the rate-limiting membrane is formulated from ethylcellulose.

Claim 5 A composition as described in Claim 1 where the pellets are adminstered in a starch capsule coated with a combination of polymethacrylates that is designed to disintegrate and release the pellets in the terminal ileum or in the colon.

Figure 1
Release of ridogrel at pH 6 and pH 7 from 0.61-0.7 mm pellets coated with 3.7% Eudragit RS (USP method 2 / 37°C)

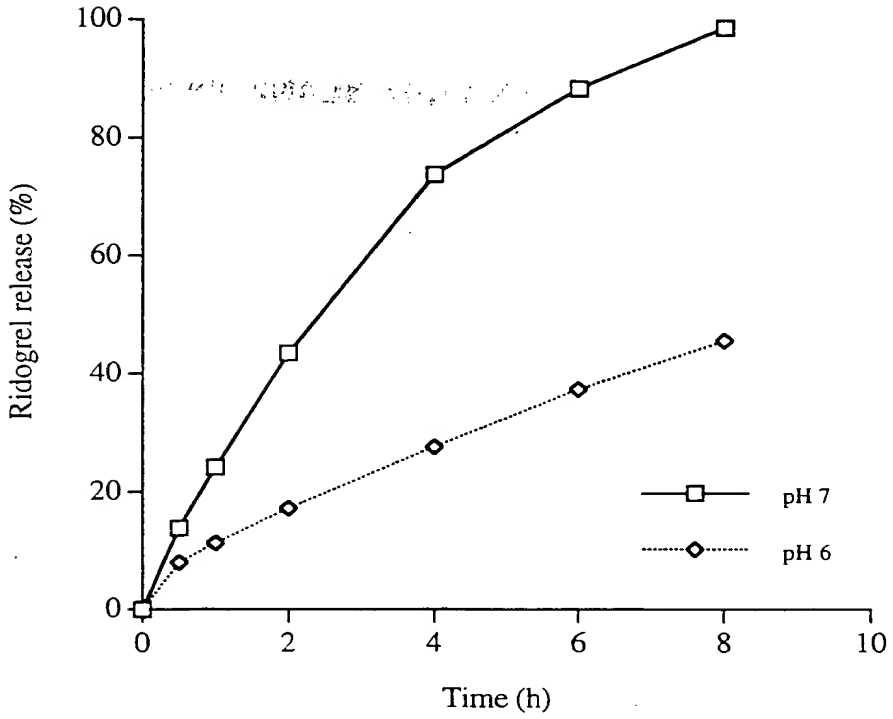
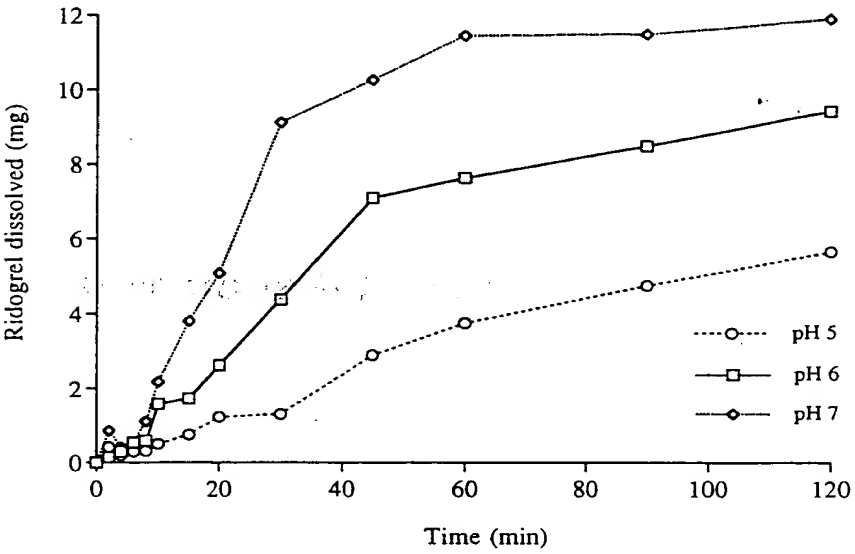


Figure 2
Dissolution of ridogrel and sodium ridogrel at pH 5, 6 and 7

a) Dissolution of ridogrel at pH 5, 6 and 7



b) Dissolution of sodium ridogrel at pH 5, 6 and 7

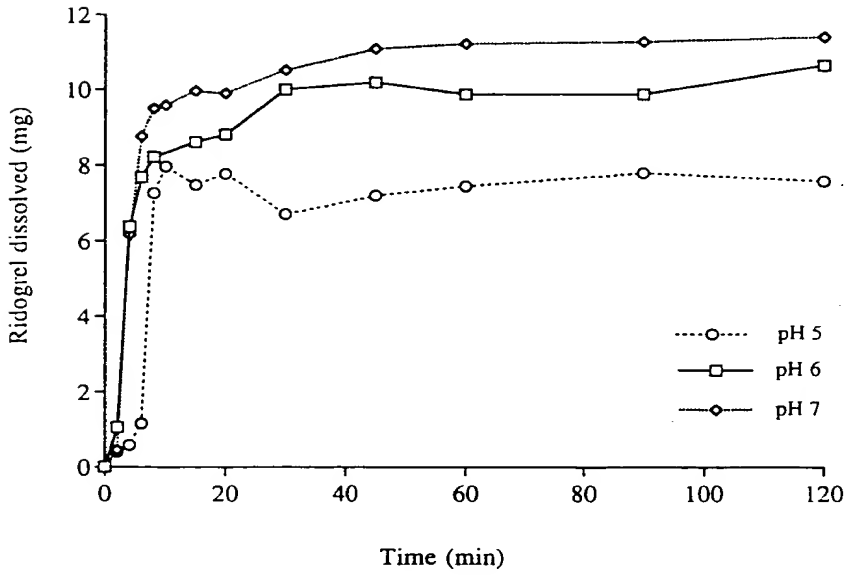


Figure 3
Release of ridogrel (as Na salt) at pH 5, 6 and 7 from 0.6-0.71 mm pellets with 19% w/w Eudragit·RS coating (USP method 2 / 37°C)

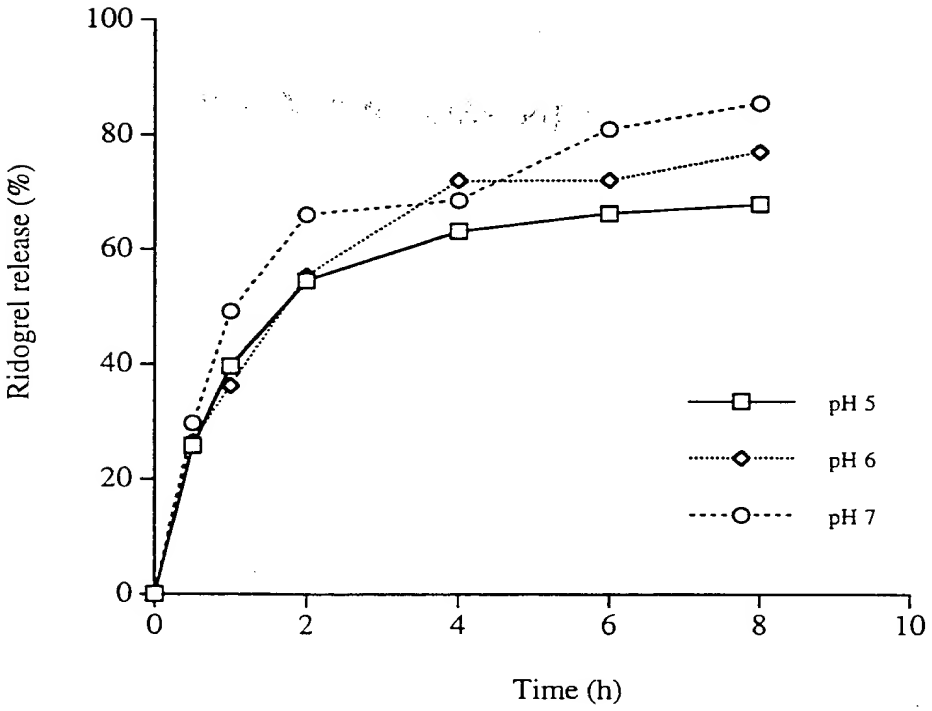


Figure 4
Release of ridogrel (as Na salt) from 1-1.18 mm pellets with three levels of Aquacoat coating (USP method 2 / 37°C)

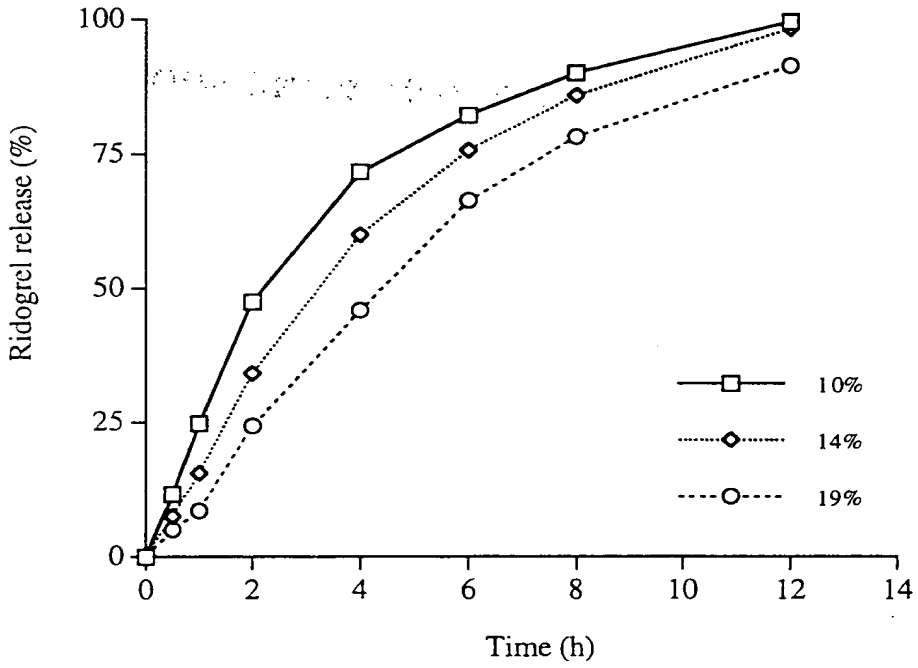
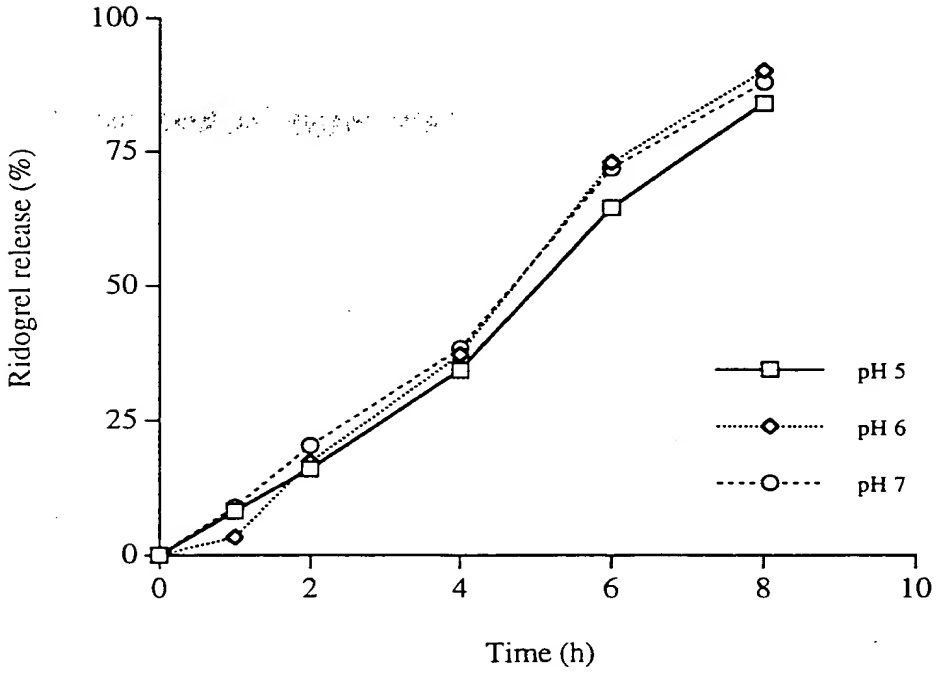


Figure 5
Release of ridogrel (as Na salt) at pH 5, 6 and 7 from 1-1.18 mm pellets containing 14% Aquacoat (USP method 2 / 37°C)



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6-10-97

Eric Potter Clarkson.